REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

As noted in the Office Action Summary, claims 1-23 are currently pending. Claims 7, 16, 17 and 19-23 stand rejected as withdrawn as directed to non-elected subject matter.

Claim 1 is amended herein to recite that the poxviral particle is an intracellular mature virus (IMV). Basis for this amendment may be found throughout the specification as-filed, including claim 4 as-filed. Thus, no new matter is introduced by way of the present Amendment. Claim 4 is canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation or divisional application directed to any subject matter canceled by way of the present Amendment.

Objections to the claims

Claim 1 is objected to for the recitation of "EEV". Claim 1 is amended herein to remove "EEV". Claim 4 is objected to for the recitation of "IMV". As the subject matter of claim 4 is added herein to claim 1, claim 1 is amended to recite the full definition of "IMV", intracellular mature virus, as recited on page 2, lines 26-28, of the specification.

Claims 4-6, 11-15 and 18 stand objected to as purportedly in improper multiple dependent format. Specifically, the Office Action states that claims 4-6, 11-

15 and 18 are multiple dependent claims which depend upon multiple dependent claims, and thus have not been examined on the merits.

To this end, Applicants submit that a Preliminary Amendment was filed by Applicants on April 12, 2001, amending the claims to remove multiple dependencies. Thus, Applicants request acknowledgement of receipt of the Preliminary Amendment of April 12, 2001. A copy is attached hereto, with the stamped postcard showing receipt of the Preliminary Amendment by the U.S. Patent and Trademark Office. The claims listed herein on pages 2-5 reflect the Preliminary Amendment. Because the multiple dependencies were previously removed in a Preliminary Amendment prior to examination on the merits, Applicants submit that rejections, if any, made in a following Office Action against claims 5-6, 11-15 and 18 should not be made final. Finally, Applicants note that claim 4, as objected to, is canceled herein. Applicants respectfully request that the Preliminary Amendment filed on April 12, 2001 be entered and acknowledged.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

Claims 9 and 10 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly failing to comply with the enablement requirement. Specifically, the Examiner asserts that the skilled artisan would have to perform undue experimentation to practice the invention as recited in claims 9 and 10. Applicants respectfully disagree.

As stated in *Ex parte Forman* (230 USPQ 546 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are quantity of experimentation necessary, amount of direction or guidance presented, presence or

absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As, the Office is aware, "[a] patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Thus, not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be. *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (Bd. Pat. App. & Int. 1992).

The Examiner asserts that claims 9-10 are not enabled, and that undue experimentation would be required to practice the claimed invention, as the working examples purportedly fail to demonstrate that a poxviral particle may retain its capacity to infect when the p14 protein is compromised by fusion to a targeting moiety. Applicants submit that the combination of what is known in the art with what is disclosed in the working examples of the specification, taken in consideration of the scope of the claims, render the claims enabled.

As base claim 1 is amended herein to recite that the poxviral particle is an intracellular mature virus (IMV), claim 9 is directed to a poxviral particle wherein the poxviral particle is one of the expression products of the A27L, L1R, A14L, A17L, D8L, and H13L genes. Claim 10 is directed to a poxviral particle where the heterologous ligand moiety is fused to the N-terminus of the expression product of the A27L gene. Thus, claims 9-10 are directed to a poxviral particle with a targeted infection specificity, using a targeting ligand fused to the p14 protein.

The Office Action states that p14 is critical to the ability of vaccinia to infect a host organism, and that fusing a targeting ligand to p14 protein would interfere with

this ability to infect. In support, the Office Action cites to Hsiao, *Journ. of Virol.* (1998) 72:8374-8379. However, Applicants note that Hsiao only discloses that the N-terminal portion of the p14 protein is important to the attachment of the vaccinia virus particle to the heparin sulfate on the cell membrane. However, Hsaio does not state that fusing a targeting ligand to the p14 protein would interfere with its ability to infect a host cell.

Beyond this citation to Hsiao, the Office Action does not provide any support or scientific reasoning in support of the assertion that the poxviral particle of the claimed invention would be inoperative when a targeting moiety is fused to the p14 terminus. In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993). A specification which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth. *See* MPEP § 2164.04.

To this end, Applicants submit that the assertion that using a targeting ligand to p14 protein would interfere with the ability of the claimed poxviral particle to infect a host organism is incorrect. The addition of the targeting moiety to the N-terminal portion of p14 would not require undue experimentation in order to make and/or use the claimed poxviral particle, as the addition of this targeting moiety would not affect the functionality of the poxviral particle. In fact, the functionality of both the virus

particle and the targeting ligand are retained. This is not unusual, as many fusion proteins are know which retain the functional activity of both original entities.

The fusion of the targeting ligand at the p14 N-terminus does not block the ability of the p14 protein to mediate virus infectivity. The use of an anti-ligand expressing cell line (*e.g.*, a MUC-1-expressing cell line as described in example 4 on pages 40-42 of the specification) is an improvement over the known technology, which allows an improvement in viral yield for large scale virus production, and which results in a of contamination of the recombinant stocks by wild-type viruses.

Claims 9-10 further stand rejected as failing to comply with the written description requirement. Specifically, the Office Action states that there are no working examples which show that a poxviral particle may retain its capacity to infect the p14 protein upon fusion to a targeting moiety. Applicants submit this is not the case.

The working examples of the specification do describe how to make and use a poxviral particle according to the present invention. Example 1 (pages 36-39 of the specification) and Example 2 (page 39) 1 describe the construction of a MVA vector targeted to MUC-1-positive cells. This construct comprises the scFv chain of the SM3 monoclonal antibody fused to the p14 N-terminus. The resulting MVA particles are constructed, isolated and propagated in conventional primary chicken embryo fibroblasts (CEFs) as are conventional recombinant MVA viruses. This is specifically described, for example, on page 39, lines 18-21 and page 41, lines 24-26 of the specification.

Several clones were also selected for additional analysis. As shown in Example 5 (pages 40-42), the majority of the selected clones do express the fusion

scFv SM3-p14 protein. Further, the targeting SM3 scFv is accessible at the virus surface since capable of interacting with a MUC-1 peptide. Moreover, the resulting poxviral particles were capable of infecting MUC-1-expressing cells with a higher efficiency than cell lines which do not express MUC-1.

Taken together, the working examples of the present specification do describe poxviral particles targeted to MUC-1 positive cells, that comprise a SM3 scFv antibody inserted at the p14 N-terminus which retain their efficacy. The SM3 scFv antibody is expressed at the virus surface and is capable of recognizing and binding its target (the MUC-1 antigen), resulting in an improved infectivity of MUC-1 positive cells.

As discussed above, Applicants submit that the claims 9-10 are enabled by the specification, as undue experimentation would not be required to make/use the invention, and that claims 9-10 are supported by written description of the specification. However, even if the fusion of a targeting ligand was detrimental to the ability of p14 to bind to cellular heparin sulfate, Applicants note that the absence of the binding to cellular heparin sulfate would not prevent the use of the presently claimed poxviral particle. Because the claimed poxviral particle is equipped with a targeting moiety that is expressed at the virus surface (*see* example 5), infection can occur via the binding to the anti-ligand moiety present at the surface of the targeted cell.

In light of the above, Applicants request that the rejection of claims 9-10 under 35 U.S.C. §112, first paragraph.

Rejections Under 35 U.S.C. § 102

Claims 1, 3 and 8 stand rejected under 35 U.S.C. § 102(a) as purportedly anticipated by Paul *et al.*, 2000, *Cancer Gene Ther.* 7, 615-623).

Applicants submit that Paul et al. fail to recite every element of the presently claimed invention, as amended herein. To anticipate a claim, a single prior art reference must teach each and every element of the claimed invention. *See* M.P.E.P. § 2131; *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987); *Hybritech Inc.v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986).

As amended herein, claim 1, from which claims 3 and 8 depend, is directed to a poxviral particle with a targeted infection specificity towards target cells, wherein the particle infects the target cells, and wherein the specificity is conferred by at least one heterologous ligand moiety which is localized at the surface of the poxviral particle and which is capable of binding an anti-ligand molecule localized at the surface of the target cells. The poxviral particle is an intracellular mature virus (IMV).

Paul et al. is directed to a vaccinia virus particle comprising a genome which has been engineered to express a therapeutic monoclonal antibody equipped with a hydrophobic transmembrane region. Upon the infection of permissive cells, the resulting poxviral particles transfer the viral genome so that the monoclonal antibody is expressed in the host cells. As a result, the membrane-anchored version of the monoclonal antibody is exposed at the surface of the infected host cells.

In contrast to the virus particle of Paul et al., the presently claimed poxviral particles have a targeting moiety (*e.g.*, a monoclonal antibody) exposed at the virus surface. This location of the targeting moiety allows the infection of target cells

expressing the corresponding anti-ligand (*e.g.*, the antigen recognized by the monoclonal antibody). Further, claim 1 is amended herein to recite the subject matter of claim 4, an IMV poxviral particle having a targeted infection specificity conferred by at least one heterologous ligand moiety which is located at the surface of said poxviral particle. An IMV particle is not recited by Paul et al., and Applicants note that claim 4, directed to an IMV particle, was not included in the present rejection.

Thus, in light of the above, Applicants request that the rejections under 35 U.S.C. § 102 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: September 16, 2004

By: _____
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VA 370300.1

Inventor: Jean-Marc BALLOUL, et al Appln. No. new application

Docket No.: 032751-052 Work Atty: TSR Date: April 12, 2001

Title: POXVIRUS WITH TARGETED INFECTION SPECIFICITY

The following was/were received in the U.S. Patent and Trademark Office on the date stamped hereon:

- ☒ Utility Patent Application Transmittal
- ☐ Design Patent Application Transmittal
- ☐ Continuing Prosecution Application Request
- ☐ Provisional Application Cover Sheet
- ☐ Provisional Application Transmittal
- ☐ Continuation/Divisional Application (Rule 1.53(b)) with copy of application
- ☐ Request for Continued Examination

INCLUDING:

- ☒ Specification (pages 1 - 43)
- ☒ Claims (claim(s) 1 - 23, 3 pgs.)
- ☒ Drawings (Fig(s). 1 - 3, 3 pgs.)
- ☒ Abstract of the Disclosure
- ☐ Executed Declaration/Power of Attorney
- ☐ Unexecuted Declaration/Power of Attorney
- ☐ Assignment/Assignment Recordation Form Cover Sheet (PTO-1595)
- ☐ Claim for Convention Priority w/_ certified copy(s)
- ☒ Preliminary Amendment
- ☐ Information Discl. Statement Transmittal Letter
- ☐ Information Disclosure Citation (PTO-1449)
- ☐ Information Disclosure Statement w/_ document(s)
- ☐ Petition for __ Month Extension of Time
- ☐ Constructive Petition for Extensions of Time
- ☐ Bibliographic Data Entry Form
- ☒ Check for $ 764.00 is enclosed
- ☐ Check for $__ is enclosed
- ☐ Charge $__ to Deposit Account
- ☒ Sequence listing & seq. disk
- ☐
- ☐
- ☐

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OIPE JC68 APR 12 2001 PATENT & TRADEMARK OFFICE

12 (10/00)

Inventor: Jean-Marc BALLOUL, et al Appln. No. new application

Docket No.: 032751-052 Work Atty: TSR Date: April 12, 2001

Title: POXVIRUS WITH TARGETED INFECTION SPECIFICITY

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- ☐ Provisional Application Cover Sheet
- ☐ Provisional Application Transmittal
- ☐ Continuation/Divisional Application (Rule 1.53(b)) with copy of application
- ☐ Request for Continued Examination

INCLUDING:

- ☒ Specification (pages 1 - 43)
- ☒ Claims (claim(s) 1 - 23, 3 pgs.)
- ☒ Drawings (Fig(s). 1 - 3, 3 pgs.)
- ☒ Abstract of the Disclosure
- ☐ Executed Declaration/Power of Attorney
- ☐ Unexecuted Declaration/Power of Attorney
- ☐ Assignment/Assignment Recordation Form Cover Sheet (PTO-1595)
- ☐ Claim for Convention Priority w/_ certified copy(s)
- ☒ Preliminary Amendment
- ☐ Information Discl. Statement Transmittal Letter
- ☐ Information Disclosure Citation (PTO-1449)
- ☐ Information Disclosure Statement w/_ document(s)
- ☐ Petition for __ Month Extension of Time
- ☐ Constructive Petition for Extensions of Time
- ☐ Bibliographic Data Entry Form
- ☒ Check for $ 764.00 is enclosed
- ☐ Check for $__ is enclosed
- ☐ Charge $__ to Deposit Account
- ☒ Sequence listing & seq. disk
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Patent
Attorney's Docket No. 032751-052

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Jean-Marc BALLOUL et al.	)	Group Art Unit: Unassigned
	)	
Application No.: New Application	)	Examiner: Unassigned
	)	
Filed: April 12, 2001	)	
	)	
For: POXVIRUS WITH TARGETED INFECTION SPECIFICITY	)	

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the above-captioned application as follows:

IN THE CLAIMS:

Kindly replace claims 1, 3-6, 10, 11, 14, 16-20 and 22, as follows.

1. (Amended) A poxviral particle having a targeted infection specificity towards target cells wherein said particle infects said target cells and wherein said specificity is conferred by at least one heterologous ligand moiety which is localized at the surface of said poxviral particle and which is capable of binding an anti-ligand molecule localized at the surface of said target cells, with the proviso that when said poxviral particle is an EEV vaccinia virus particle said ligand is not an antibody directed to ErbB-2.

3. (Amended) The poxviral particle of claim 1, wherein said vaccinia virus is selected from the group consisting of Copenhagen, Wyeth and Ankara modified (MVA) strains.

4. (Amended) The poxviral particle of claim 1, wherein said poxviral particle is an IMV.

5. (Amended) The poxviral particle of claim 1, wherein said target cells are tumoral cells and said heterologous ligand moiety is capable of binding a tumor-specific antigen, a cellular protein differentially or overexpressed onto said tumoral cells or a gene product of a cancer-associated virus.

6. (Amended) The poxviral particle of claim 1, wherein said heterologous ligand moiety is a fragment of an antibody capable of recognizing and binding to the MUC-1 antigen.

10. (Amended) The poxviral particle of claim 8, wherein said heterologous ligand moiety is fused to the N-terminus of the expression product of the A27L gene.

11. (Amended) The poxviral particle of claim 1, wherein said heterologous ligand moiety comprises a signal peptide facilitating its insertion in the envelope of said poxviral particle.

14. (Amended) The poxviral particle of claim 1, wherein said poxviral particle comprises at least a nucleic acid of interest.

16. (Amended) A vector comprising at least one nucleotide sequence encoding a chimeric protein comprising (i) at least an heterologous ligand moiety as defined in claim 1, and (ii) all or part of an homologous viral polypeptide naturally localized at the surface of a poxviral particle.

17. (Amended) The vector of claim 16 wherein said homologous viral polypeptide is selected from the group consisting of the expression products of the A27L, L1R, A14L, A17L, D8L and H3L genes.

18. (Amended) A composition comprising at least one poxviral particle of claim 1 and a pharmaceutically acceptable vehicle.

19. (Amended) A method for the treatment of a human or animal organism by gene therapy comprising administering an effective amount of the poxviral particle according to claim 1 to a human or animal in need of such treatment.

20. (Amended) A method for the purification of a poxviral particle of claim 1 from a viral preparation containing both said poxviral particle and a wild type poxviral particle, comprising the steps of binding said viral preparation to a solid support coated

with an antiligand molecule capable of binding said heterologous ligand moiety and recovering said poxviral particle.

22. (Amended) The method according to claim 20, further comprising the step of infecting a permissive cell with said recovered poxviral particle.

REMARKS

Entry of the foregoing Amendment is respectfully requested.

Should the Examiner have any questions concerning the subject application, a telephone call to the undersigned would be appreciated.

Respectfully submitted,

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Date: April 12, 2001

Attachment to Preliminary Amendment dated April 11, 2001

Marked-up Claims 1, 3-6, 10, 11, 14, 16-20 and 22

1. (Amended) A poxviral particle having a targeted infection specificity towards target cells wherein said particle infects [preferably] said target cells and wherein said specificity is conferred by at least one heterologous ligand moiety which is localized at the surface of said poxviral particle and which is capable of binding an anti-ligand molecule localized at the surface of said target cells, with the proviso that when said poxviral particle is an EEV vaccinia virus particle said ligand is not an antibody directed to ErbB-2.

3. (Amended) The poxviral particle of claim 1 [or 2], wherein said vaccinia virus is selected from the group consisting of Copenhagen, Wyeth and Ankara modified (MVA) strains.

4. (Amended) The poxviral particle of [any of claims 1 to 3] claim 1, wherein said poxviral particle is an IMV.

5. (Amended) The poxviral particle of [any of claims 1 to 4] claim 1, wherein said target cells are tumoral cells and said heterologous ligand moiety is capable of binding a tumor-specific antigen, a cellular protein differentially or overexpressed onto said tumoral cells or a gene product of a cancer-associated virus.

Attachment to Preliminary Amendment dated April 11, 2001

Marked-up Claims 1, 3-6, 10, 11, 14, 16-20 and 22

6. (Amended) The poxviral particle of [any of claims 1 to 5] claim 1, wherein said heterologous ligand moiety is a fragment of an antibody capable of recognizing and binding to the MUC-1 antigen.

10. (Amended) The poxviral particle of claim 8 [or 9], wherein said heterologous ligand moiety is fused to the N-terminus of the expression product of the A27L gene.

11. (Amended) The poxviral particle of [any of claims 1 to 10] claim 1, wherein said heterologous ligand moiety comprises a signal peptide facilitating its insertion in the envelope of said poxviral particle.

14. (Amended) The poxviral particle of [any of claims 1 to 13] claim 1, wherein said poxviral particle comprises [comprises] at least a nucleic acid of interest.

16. (Amended) A vector comprising at least one nucleotide sequence encoding a chimeric protein comprising (i) at least an heterologous ligand moiety as defined in [any of claims 1 and 5 to 8] claim 1, and (ii) all or part of an homologous viral polypeptide naturally localized at the surface of a poxviral particle.

Attachment to Preliminary Amendment dated April 11, 2001

Marked-up Claims 1, 3-6, 10, 11, 14, 16-20 and 22

17. (Amended) The vector of claim 16 wherein said homologous viral polypeptide is [as defined in claim 9] selected from the group consisting of the expression products of the A27L, L1R, A14L, A17L, D8L and H3L genes.

18. (Amended) A composition comprising at least one poxviral particle of [any of claims 1 to 15 or at least one vector of claim 16 or 17] claim 1 and a pharmaceutically acceptable vehicle.

19. (Amended) [Use of a poxviral particle of any of claims 1 to 15 or of a vector of claim 16 or 17 for the preparation of a drug intended] A method for the treatment of a human or animal organism by gene therapy comprising administering an effective amount of the poxviral particle according to claim 1 to a human or animal in need of such treatment.

20. (Amended) A method for the purification of a poxviral particle of [any of claims 1 to 15] claim 1 from a viral preparation containing both said poxviral particle and a wild type poxviral particle, comprising the steps of binding said viral preparation to a solid support coated with an antiligand molecule capable of binding said heterologous ligand moiety and recovering said poxviral particle.

Attachment to Preliminary Amendment dated April 11, 2001

Marked-up Claims 1, 3-6, 10, 11, 14, 16-20 and 22

22. (Amended) The method according to claim 20 [or 21], further comprising the step of infecting a permissive cell with said recovered poxviral particle.